INNOVATIONS IN THE TREATMENT OF PULMONARY HYPERTENSION

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### Relevant financial disclosures: previous 12 months

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<thead>
<tr>
<th>Affiliation/Financial Interest</th>
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He Has New Heart, Lungs

PITTSBURGH (AP) — A 29-year-old Baptist minister from South Carolina who underwent a heart and lung transplant operation left the hospital Thursday with plans for a relaxing shower and a fancy restaurant meal.

"I feel great. I’m on top of the world," the Rev. Gary Crismond said, adding, "I can’t run a mile or anything, I’m still rather weak."

Crismond said he has been "pretty well confined to my [hospital] room or the hallway. So I’m looking forward to just getting out and doing things whenever I want to. Going out to dinner sounds very appealing."

The Taylors, S.C. minister underwent the 9 1/2-hour operation in September, becoming the ninth person ever to undergo the rare heart and lung transplant operation.

Crismond Gets Hug From Wife Tamra At Hospital
Pulmonary Hypertension: Where Are We in 1985?

Senior Assistant Resident Lecture

Victor F. Tapson, MD
1. Pulmonary arterial hypertension
2. PH due to left heart disease
3. PH due to lung diseases and/or hypoxia
4. Chronic thromboembolic PH
5. PH with unclear multifactorial mechanisms

Pulmonary Arterial Hypertension

1. Pulmonary arterial hypertension

1.1 Idiopathic PAH

1.2 Heritable PAH

1.2.1 BMPR2

1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3

1.2.3 Unknown

1.3 Drug and toxin induced

1.4 Associated with:

1.4.1 Connective tissue disease

1.4.2 HIV infection

1.4.3 Portal hypertension

1.4.4 Congenital heart diseases

1.4.5 Schistosomiasis

1’ PVOD and/or PCH

1” Persistent PH of the newborn (PPHN)
1. Pulmonary Arterial Hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
     1.2.1 BMPR2
     1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
     1.2.3 Unknown
   1.3 Drug and toxin induced
   1.4 Associated with:
     1.4.1 Connective tissue disease
     1.4.2 HIV infection
     1.4.3 Portal hypertension
     1.4.4 Congenital heart diseases
     1.4.5 Schistosomiasis
   1' PVOD and/or PCH
   1" Persistent PH of the newborn (PPHN)

2. PH Due to Left Heart Disease
   2.1 Left ventricular systolic dysfunction
   2.2 Left ventricular diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital CMs

3. PH Due to Lung Diseases and/or Hypoxia
   • 3.1 Chronic obstructive pulmonary disease
   • 3.2 Interstitial lung disease
   • 3.3 Pulmonary diseases with mixed restriction / obstruction
   • 3.4 Sleep-disordered breathing
   • 3.5 Alveolar hypoventilation disorders
   • 3.6 Chronic exposure to high altitude
   • 3.7 Developmental lung diseases

4. Chronic Thromboembolic PH

5. PH With Unclear Multifactorial Mechanisms
   • 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   • 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, LAM
   • 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   • 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

In PAH-Queri, 42.7% of patients with proven PH did not get VQ scan.

Novel signaling pathways in pulmonary arterial hypertension (2015 Grover Conference Series)

Keytam S. Awad, 1 James D. West, 2 Vinicio de Jesus Perez, 3 Margaret MacLean 4

1 Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA; 2 Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; 3 Department of Medicine, Stanford University, Stanford, California, USA; 4 Research Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom

Abstract: The proliferative endothelial and smooth muscle cell phenotype, inflammation, and pulmonary vascular remodeling are prominent features of pulmonary arterial hypertension (PAH). Mutations in bone morphogenetic protein type 2 receptor (BMPR2) have been identified as the most common genetic cause of PAH and females with BMPR2 mutations are 2.5 times as likely to develop heritable forms of PAH than males. Higher levels of estrogen have also been observed in males with PAH, implicating sex hormones in PAH pathogenesis. Recently, the estrogen metabolite 16α-OHE1 (hydroxyestrone) was implicated in the regulation of miR29, a microRNA involved in modulating energy metabolism. In females, decreased miR96 enhances serotonin’s effect by upregulating the 5-hydroxytryptamine 1B (5HT1B) receptor. Because PAH is characterized as a quasi-malignant disease, likely due to BMPR2 loss of function, altered signaling pathways that sustain this cancer-like phenotype are being explored. Extracellular signal–regulated kinases 1 and 2 and p38 mitogen-activated protein kinases (MAPKs) play a critical role in proliferation and cell motility, and dysregulated MAPK signaling is observed in various experimental models of PAH. Wnt signaling pathways preserve pulmonary vascular homeostasis, and dysregulation of this pathway could contribute to limited vascular regeneration in response to injury. In this review, we take a closer look at sex, sex hormones, and the interplay between sex hormones and microRNA regulation. We also focus on MAPK and Wnt signaling pathways in the emergence of a proproliferative, antiapoptotic endothelial phenotype, which then orchestrates an angioproliferative process of vascular remodeling, with the hope of developing novel therapies that could reverse the phenotype.

Keywords: vascular remodeling, sex hormones, microRNA, mitogen-activated protein kinase, Wnt.

Favors Treatments  | Favors Controls
---|---
Figure 1. Summary of estrogen metabolism and select signaling pathways of key interest. See text for details. CYP: cytochrome P450; 16α-OHE1: 16α-hydroxyestrone.
Targets for Current Therapies in PAH

**Prostacyclin Pathway**
- Arachidonic Acid
  - Prostacyclin Synthase
    - Prostacyclin
      - cAMP
        - Prostacyclin Derivatives

**Endothelin Pathway**
- Big Endothelin
  - Endothelin-converting Enzyme
    - Endothelin-1
      - Endothelin Receptor Antagonists
        - Endothelin Receptor A
        - Endothelin Receptor B

**Nitric Oxide Pathway**
- Arginine
  - Nitric Oxide Synthase
    - Nitric Oxide
      - Exogenous Nitric Oxide
      - Phosphodiesterase Type-5
        - cGMP

**Nitric Oxide Pathway**
- cGC Stimulator
  - sGC
  - cGMP

**Prostacyclin Pathway**
- Vasoconstriction and Proliferation

**Endothelin Pathway**
- Vasoconstriction and Proliferation

**Nitric Oxide Pathway**
- Vasodilation and Antiproliferation

Classification of PAH Medications

**Less severely ill**

- Calcium channel blockers (vasodilator responder)
- Endothelin receptor antagonists
  - Bosentan (Tracleer) Ambrisentan (Letairis) Macitentan (Opsumit)
- PDE-5 inhibitors
  - Sildenafil (Revatio) Tadalafil (Adcirca) Riociguat (Adempas)

**More severely ill**

- Prostanoid therapy
  - Oral – Treprostinil (Orenitram)
  - Inhaled - Iloprost (Ventavis), treprostinil (Tyvaso)
  - SC treprostinil (Remodulin)
  - IV - Epoprostenol (Flolan / Veletri), treprostinil (Remodulin)

QUESTION 1:

Which of the following statements is true?

A. The mortality of PAH has decreased over the past 3 decades

B. The mortality of PAH has increased over the past 3 decades

C. The mortality of PAH has remained unchanged

D. All oral therapies have proven to improve one year mortality
Observed vs predicted survival using the NIH, French, PHC and REVEAL equations.

THE PROBLEM
QUESTION 2:

If Hillary Clinton and Donald Trump are in a boat and it capsizes, who survives?

AMERICA!

QUESTION 3:

Why does Donald Trump take Xanax?

For Hispanic attacks... .
Future Directions in PAH:

- “Induction therapy”
- Computer modeling of pulmonary vasculature and RV
- Pharmacogenomics
- Inflammation
- Epigenetics / apoptosis – Cancer lessons applied to PAH
- Endothelial progenitor cells
- Pulmonary artery denervation
- Cardiac regeneration / angiogenesis
- Xenotransplantation
- Animal models
- New drug therapy
Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension


ABSTRACT

BACKGROUND
Data on the effect of initial combination therapy with ambrisentan and tadalafil on long-term outcomes in patients with pulmonary arterial hypertension are scarce.

METHODS
In this event-driven, double-blind study, we randomly assigned, in a 2:1:1 ratio, participants with World Health Organization functional class II or III symptoms of pulmonary arterial hypertension who had not previously received treatment to receive initial combination therapy with 10 mg of ambrisentan plus 40 mg of tadalafil (combination-therapy group), 10 mg of ambrisentan plus placebo (ambrisentan-placebo group), or placebo plus tadalafil (tadalafil-placebo group).
A Combination Therapy vs. Pooled Monotherapy

- **Combination therapy**
- **Pooled monotherapy**

**Hazard ratio, 0.50 (95% CI, 0.35–0.72)**

P < 0.001

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**No. at Risk**

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Selexipag for the Treatment of Pulmonary Arterial Hypertension

Olivier Sitbon, M.D., Richard Channick, M.D., Kelly M. Chin, M.D.,
Aline Frey, Pharm.D., Sean Gaine, M.D., Nazzareno Galiè, M.D.,
Hossein-Ardeschir Ghofrani, M.D., Marius M. Hoeper, M.D., Irene M. Lang, M.D.,
Ralph Preiss, M.D., Lewis J. Rubin, M.D., Lilla Di Scala, Ph.D., Victor Tapson, M.D.,
Igor Adzerikho, M.D., Jinming Liu, M.D., Olga Moiseeva, M.D., Xiaofeng Zeng, M.D.,
Gérald Simonneau, M.D., and Vallerie V. McLaughlin, M.D.,
for the GRIPHON Investigators*

ABSTRACT

BACKGROUND

In a phase 2 trial, selexipag, an oral selective IP prostacyclin-receptor agonist, was shown to be beneficial in the treatment of pulmonary arterial hypertension.

METHODS

December 24, 2015
Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

Olivier Sitbon, Xavier Jais, Laurent Savale, Vincent Cottin, Emmanuel Bergot, Elise Artaud Macari, Hélène Bouvaist, Claire Dauphin, François Picard, Sophie Builhon, David Montani, Marc Humbert, Gérard Simonneau

Data from newly diagnosed NYHA FC III/IV PAH patients (n=19) initiated on upfront triple combination therapy (intravenous epoprostenol, bosentan and sildenafil) were collected retrospectively from a prospective registry.

Significant improvements in 6-min walk distance and haemodynamics were observed after 4 months’ triple combination therapy in 18 patients (p<0.01); 17 patients had improved to NYHA FC I or II. One patient was not included in the month...
Three oral therapies up front vs. two:

- Adcirca
- Macitentan
- Selexipag vs. Adcirca / Macitentan
RALINEPAG (ADP-811)

New, selexipag-like drug...

- (Arena Pharmaceuticals) - an oral potent and selective, non-prostanoid, IP receptor agonist.
- 25 h half-life — once or twice daily dosing with escalation.
- Open-label pilot study followed by a D-B, randomized, parallel-group, P-C Phase 2 Trial
- 6 week dose titration ñ 12 week treatment phase
A systematic review and meta-analysis of trials using statins in pulmonary arterial hypertension

Vidhu Anand, Sushil Garg, Sue Duval, Thenappan Thenappan

Cardiovascular Division, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA

Abstract: Statins improve pulmonary vascular remodeling and right ventricular hypertrophy in animal models of pulmonary arterial hypertension (PAH). However, clinical trials assessing the efficacy of statins in patients with PAH have reported mixed results. In this systematic review and meta-analysis, we assess the efficacy of statins in patients with PAH. We included randomized controlled clinical trials (RCTs) that evaluated the efficacy of statins in patients with PAH. Primary outcomes were mortality and change in 6-minute walk distance (6MWD), binary and continuous endpoints, and 32.7% of patients were assigned to treatment arms (70% were assigned to placebo). The pooled analysis showed a significant improvement in 6MWD (WMD: 32.7 [95% CI: 22.7 to 42.7]), 6MWD (WMD: 9.27 [95% CI: −27.73 to 9.20]), or cardiac index (WMD: 0.11 [95% CI: −0.04 to 0.27]) with statin therapy when compared to placebo. There was no difference in adverse events leading to withdrawal of therapy between statin and placebo groups. These data suggest that statins are not beneficial in the treatment of PAH. There is a need for large, well-conducted clinical trials assessing the effects of statins in patients with PAH. Future trials should include homogeneous patient populations and should be long-term, event-driven trials with combined morbidity and mortality end points.

Keywords: right ventricle, hemodynamics, vascular remodeling, pulmonary embolism.

Pulm Circ 2016;6(3):295-301. DOI: 10.1086/687304.

“These data suggest that statins are not beneficial in PAH”
Phase I safety study of ranolazine in pulmonary arterial hypertension

Mardi Gombe,1 Vasiliki Thomeas,1,2 Hunter Gillies,3 Ronald J. Oudiz3

1Section of Cardiology, Department of Medicine, University of Chicago, Chicago, Illinois, USA; 2Committee on Clinical Pharmacology and Pharmacogenomics, Department of Medicine, University of Chicago, Chicago, Illinois, USA; 3Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, School of Medicine, Case Western University, Cleveland, Ohio, USA; 4Gilead Sciences, Foster City, California, USA; 5Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA

Abstract: Pulmonary arterial hypertension (PAH) causes right ventricular ischemia, dysfunction, and failure. PAH patients may benefit from antianginal agents based on a shared pathophysiology with left ventricular ischemia. A single-center, randomized, placebo-controlled trial (1:1) to assess the acute vasoreactivity and safety of ranolazine in PAH was conducted. Plasma samples for pharmacokinetic (PK) studies were drawn during hemodynamic measurements at 0, 60, 90, 120, 240, and 360 minutes from a Swan-Ganz catheter. All patients received 500-mg doses, uptitrated to 1,000 mg at week 4, monthly evaluations, and a complete objective assessment after 12 weeks, followed by an open-label extension. Thirteen patients were randomized and 12 enrolled (6 ranolazine, 6 placebo). All patients completed the acute phase; 10 completed the 12-week study. There were no acute changes in invasive hemodynamics. At 12 weeks ranolazine was well tolerated. Only 1 of the 5 patients on ranolazine had a serum concentration considered to be in the therapeutic range. Two serious adverse events required early withdrawal (both in the ranolazine group); gastrointestinal complaints were the most common adverse event. Efficacy measures did not differ significantly, although 2 of the 4 patients on ranolazine had better exercise capacity.

"Ranolazine did not consistently reach therapeutic levels. Future studies should perform PK analysis in PAH patients and explore the safety / tolerability of higher doses."

Dose-dependent, therapeutic potential of angiotensin-(1–7) for the treatment of pulmonary arterial hypertension

Siegfried Breitling,1,2 Adrienn Krauszman,1,3 Richa Parihar,1 Thomas Walther,4 Mark K. Friedberg,5 Wolfgang M. Kuebler1,5,6

"The reported moderate attenuation of PAH does not confirm the previously postulated high promise of this strategy."

Abstract: The effects of the heptapeptide angiotensin-(1–7) (Ang-(1–7)), via its receptor Mas, oppose many of the effects of the classic angiotensin II signaling pathway, and pharmacological exploitation of this effect is currently actively pursued for a wide range of cardiovascular, neoplastic, or immunological disorders. On the basis of its vasodilatory and antiproliferative properties, Ang-(1–7) has consequently also been proposed as a novel therapeutic strategy for the treatment of pulmonary arterial hypertension (PAH). In this study, we tested the effectiveness of Ang-(1–7) and its stable, cyclic analog cAng-(1–7) over a range of doses for their therapeutic potential in experimental PAH. In the monocrotaline (MCT) rat model of PAH, Ang-(1–7) or cAng-(1–7) were injected in doses of 30, 100, 300, or 900 μg kg⁻¹ day⁻¹, and effects on pulmonary hemodynamics and vascular remodeling were assessed. Five weeks after MCT injection, right ventricular systolic pressure (RVSP) was significantly reduced for 3 dose groups treated with Ang-(1–7) (100, 300, and 900 μg kg⁻¹ day⁻¹) and for all dose groups treated with cAng-(1–7), as compared to untreated controls, yet the total reduction of RVSP was <50% at best and thus markedly lower than that with a positive treatment control with ambrisentan. Medial-wall thickness in pulmonary arterioles was only slightly reduced, without reaching significance, for any of the tested Ang-(1–7) compounds and doses. The reported moderate attenuation of PAH does not confirm the previously postulated high promise of this strategy, and the therapeutic usefulness of Ang-(1–7) may be limited in PAH relative to that in other cardiovascular diseases.

Keywords: pulmonary hypertension, vascular remodeling, renin-angiotensin system.

Inflammation and Immunity in the Pathogenesis of Pulmonary Arterial Hypertension

Marlene Rabinovitch, Christophe Guignabert, Marc Humbert, Mark R. Nicolls

Abstract: This review summarizes an expanding body of knowledge indicating that failure to resolve inflammation and altered immune processes underlie the development of pulmonary arterial hypertension. The chemokines and cytokines implicated in pulmonary arterial hypertension that could form a biomarker platform are discussed. Preclinical studies that provide the basis for dysregulated immunity in animal models of the disease are reviewed. In addition, we present therapies that target inflammatory/immune mechanisms that are currently enrolling patients, and discuss others in development. We show how genetic and metabolic abnormalities are inextricably linked to dysregulated immunity and adverse remodeling in the pulmonary arteries. (Circ Res. 2014;115:165-1745.)

Key Words: hypertension, pulmonary, leukotriene B4

Pulmonary arterial hypertension (PAH) is a progressive cardiopulmonary disease in which extensive oblitative changes are prevalent in the small to mid-sized pulmonary arteries. Alterations in structure and function of the endothelium occur in conjunction with growth of neointimal, medial, and adventitial layers, culminating in an obliterative arteriopathy associated with high resistance to blood flow and right heart failure and death. Currently approved PAH therapies focus on dilating the partially occluded vessels and are weak antiproliferative agents. However, they have not resulted in a strategy that is effective in reversing vascular remodeling and preventing deterioration and the need for a lung transplant. In recent years, greater attention has been focused on the frequently observed perivascular inflammation in patients with all forms of PAH, from idiopathic (I) PAH to PAH associated with systemic autoimmune diseases.\(^\text{1,2}\) An expanding body of knowledge has related genetic susceptibility, inflammation, and metabolic (glycolytic) shifts in vascular cells to PAH pathogenesis. In fact, the inflammatory processes are inextricably linked to altered vascular and inflammatory cell metabolism.\(^\text{3}\) Thus, there is a strong rationale to identify genetic factors that predispose to impaired resolution of inflammation and to determine how immune-mediated vascular injury initiates and propagates alterations in metabolic function and in the phenotype of PAH vascular cells. Based on clinical and animal studies, described below, there is now reason to suggest that advanced vascular remodeling may be reversed by approaches that address specific inflammatory and immune processes.
• BMPR2 signaling is important because of the protective nature of this pathway.
• BMPR2 mutations are present in >70% of familial and 25% of sporadic IPAH.
• Loss of BMPR2 receptor function is key in PAH, but dysfunction of the BMPR2 receptor alone is insufficient to cause PAH.
• So, an insult may incite PAH in patients with BMPR2 dysfunction.

BMPR2 is a member of the TGF-β superfamily...
• In endothelial cells, BMPR2 activates PPARγ which induces production of the "endothelial cell survival gene" apelin by PA ECs.

Endogenous nitro-fatty acids* are highly effective in inducing PPARγ activity.....and are known for their anti-inflammatory properties.

* Olives, avocado, etc

Could apelin be used to treat PAH?
Apelin improves cardiac output in patients with pulmonary arterial hypertension

Abstract

**Background:** Apelin is an endogenous peptide of the APJ receptor that has physiological actions in the cardiovascular system and is abundantly expressed in the pulmonary vasculature. Pre-clinical models and preliminary clinical data indicate that apelin deficiency may mediate, or contribute to, the pathogenesis of pulmonary arterial hypertension (PAH). Apelin can modulate vasomotor tone and is one of the most potent endogenous inotropes yet described.

**Aims and objectives:** We aimed to investigate the effects of apelin in patients with PAH and its effects on their pulmonary circulation.
Dysfunctional BMPR2 signaling is implicated in the pathogenesis of PAH.

We used a transcriptional high-throughput luciferase reporter assay to screen 3,756 FDA-approved drugs and bioactive compounds for induction of BMPR2 signaling.

Best response achieved with FK506 (tacrolimus), via a dual mechanism of action as a calcineurin inhibitor that also binds FKBP12, a repressor of BMP signaling.

Low-dose FK506 reversed dysfunctional BMPR2 signaling in PA ECs from IPAH patients.

Low-dose FK506 reversed severe PAH in several rat PAH models including monocrotaline, VEGF receptor blockade, and chronic hypoxia.

"We recently reported that ACTIVATION of the mammalian target of rapamycin (mTOR) plays a key role in increased energy generation and maintenance of the proliferative, apoptosis-resistant PASM phenotype in human PAH."

"We report that mTOR INHIBITION attenuated or reversed the majority of the PAH-specific abnormalities in lipogenesis, glycosylation, glutathione, and NAD metabolism."
“Our data demonstrate a critical role of mTOR in major PAH metabolic abnormalities worthy of future investigation.”
Good versus Evil?

Nrf2

- The Nuclear Factor-E2-related factor 2 (Nrf2) transcription factor is critical for endogenous detoxification and free radical scavenging.
- Activation of Nrf2, thus, protects tissues from inflammation - it suppresses inflammatory signaling pathways.
- Activated macrophages express high levels of Nrf2.

NF-κB

Nuclear Factor – kappa light-chain activator of B cells

The NF-κB pathway regulates PROinflammatory cytokine production, leukocyte recruitment, and cell survival as well as contributing to the maintenance of the inflammatory response through persistent leukocyte activation.

INCORRECT activation leads to problems....
• In preclinical models, bardoxolone appears to activate Nrf2 and block NF-κB, which results in:

- Energy and ATP production
- Reductive capacity
- Vasodilation
- Apoptosis

- Inflammation
- Cell proliferation
- Lipid deposition
- Insulin resistance
- Oxidative stress

Nrf2 = nuclear factor-erythroid 2-related factor 2; NF-κB = nuclear factor kappa-B.
Bardoxolone Methyl - LARIAT

- PAH – FC II and III
- 16 week study
- Phase 2 – Three doses
- Either 1 or 2 background PAH drugs
- Primary endpoint = 6MWD
LTB₄ is Secreted by Macrophages
Leads to Endothelial Cell Death & Arterial Smooth Muscle Proliferation
LTB$_4$ is an Eicosanoid secreted by macrophages
Produced via a distinct pathway

- A pro-inflammatory mediator
- Recruits and activates neutrophils, monocytes, eosinophils
- Stimulates production of pro-inflammatory cytokines
- Elevated levels in a number of inflammatory diseases
It has been demonstrated in PAH that:

- LTB₄ levels are elevated in both animal models and human PAH lung and serum
- LTB₄ is a leukocyte attractant
- LTB₄ causes pulmonary arterial endothelial cell apoptosis (lumen)
- LTB₄ induces pulmonary smooth muscle cell proliferation (wall)

Targeted Inhibition of LTA₄ Hydrolase (LTA₄ → LTB₄):

- Inhibits LTB₄ production - implicated in endothelial injury
- Limits leukocyte migration to the site - a cause of LTB₄ production
- Prevents pulmonary arterial endothelial cell death
- Prevents pulmonary arterial smooth muscle cell proliferation

Tian et al., Science Transl Med 2013
Ubenimex (Bestatin™)
Nippon Kayaku, Japan

- LTA₄H⁺ inhibitor, aminopeptidase inhibitor (thus LTB₄ inhibitor)
- Orally active, small molecule
- Approved in Japan in 1987: adjuvant for non-lymphocytic leukemia
  - Antiproliferative, immunomodulatory
  - Marketed in 30mg QD Capsules
  - Safe and well tolerated
- Never introduced in the US or EU
- Well characterized

*Epoxide hydrolase that catalyzes the final step in the biosynthesis of the proinflammatory mediator leukotriene B₄. Has also aminopeptidase activity.
Ubenimex (UB) Reduces Lung Inflammation
Reduction in Inflammatory Markers

Inflammation is inhibited!!
PAH Models: Summary
Positive Results

- 3 PAH Animal Models Tested
  - SU5416 (VEGF) + Hypoxia
  - SU5416 (VEGF) in Athymic Rats
  - Monocrotaline (+ independently confirmed)

- Inhibition of LTB4 in PAH models:
  - Improves pressures
  - Improves survival
  - All animals benefit; earlier treatment = better results

Treatment effect correlates with levels of $\text{LTB}_4$

$$\text{LTB}_4^{\text{Athymic}} > \text{LTB}_4^{\text{MCT}} > \text{LTB}_4^{\text{SU/Hypoxia}}$$
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of UBE nimex in Patients with Pulmonary ARTerial HYpertension (WHO Group 1)

Eiger Biopharmaceuticals
Review Article

The emerging role of epigenetics in pulmonary arterial hypertension: an important avenue for clinical trials (2015 Grover Conference Series)

Jessica H. Huston¹ and John J. Ryan²

¹Department of Medicine, Salt Lake City Veterans Affairs Medical Center, Salt Lake City, Utah, USA
²Division of Cardiovascular Medicine, Department of Medicine, University of Utah, Salt Lake City, Utah, USA

Address correspondence to Dr. Jessica H. Huston, Department of Medicine, Salt Lake City Veterans Affairs Medical Center, 500 Foothill Drive, Salt Lake City, UT 84148, USA. E-mail: harris.jess@me.com.
There is evidence that epigenetic control of gene expression plays a significant role in PAH.

The three types of epigenetic modification include:

1. DNA methylation
2. Histone modification
3. RNA interference.

All three have been shown to be involved in the development of PAH.

Currently, the enzymes that perform these modifications are the primary targets of neoplastic therapy.

These targets are starting to be explored for therapies in PAH, mostly in animal models.
Methylation of DNA and histones causes nucleosomes to pack tightly together. Transcription factors cannot bind the DNA, and genes are not expressed.

Histone acetylation results in loose packing of nucleosomes. Transcription factors can bind the DNA and genes are expressed.
Histone Deacetylation Inhibition in Pulmonary Hypertension: Clinical Perspective

by Lan Zhao, Chien-Nien Chen, Nabil Hajji, Eduardo Oliver, Emanuele Cotroneo, John Wharton, Daren Wang, Min Li, Timothy A. McKinsey, Kurt R. Stenmark, and Martin R. Wilkins

- Epigenetic programming, dynamically regulated by histone acetylation, is a key mechanism regulating cell proliferation and survival.

- The data in this study come from end-stage human PAH, a rodent model, and cells in culture.

We should we try to inhibit HDAC...

Valproate can inhibit histone deacetylation...
Valproate has been found to affect signaling systems like the Wnt/beta-catenin and ERK pathways and to interfere with inositol and arachidonic acid metabolism.

Valproate also produces marked alterations in the expression of multiple genes, involved in: transcription regulation, cell survival, ion homeostasis, cytoskeletal modifications and signal transduction.
MicroRNAs are involved in multiple cellular responses during normal development and disease; they act as posttranscriptional regulators to fine-tune protein synthesis.

Evidence has emerged for a key role for miRNA in regulation of the cellular processes involved in PAH.

miR-214 stem loop loss leads to abnormal RV function and may contribute to RV failure in PAH.
Conclusions: Stable decreases in miR-124 expression contribute to an epigenetically reprogrammed, highly proliferative, migratory, and inflammatory phenotype of hypertensive pulmonary adventitial fibroblasts. Thus, therapies directed at restoring miR-124 function, including histone deacetylase inhibitors, should be investigated.


Cellular Biology

MicroRNA-124 Controls the Proliferative, Migratory, and Inflammatory Phenotype of Pulmonary Vascular Fibroblasts

Table 2. MicroRNAs identified as involved in PAH

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA-124</td>
<td>Decreased levels in proliferating PA fibroblasts; overexpression contributes to mitotic arrest</td>
<td>40</td>
</tr>
<tr>
<td>miRNA-424/503</td>
<td>Involved in the apelin pathway regulating FGF2 and PAEC proliferation</td>
<td>41</td>
</tr>
<tr>
<td>miRNA-204</td>
<td>Suppresses BRD4 expression, which regulates multiple oncogenes; normally downregulated in hypoxia</td>
<td>42, 43</td>
</tr>
<tr>
<td>miRNA-126</td>
<td>Decreased expression in decompensated right ventricular failure; expression upregulated in plexiform lesions</td>
<td>44, 45</td>
</tr>
<tr>
<td>miRNA-145/143</td>
<td>Involved in PASMC migration and apoptosis, higher expression in concentric hypertrophy vs. plexiform lesions</td>
<td>45</td>
</tr>
<tr>
<td>miRNA-17/92</td>
<td>Increased proliferation and decreased apoptosis, involved in the BMPR2 mutation pathway</td>
<td>46, 47</td>
</tr>
<tr>
<td>miRNA-21</td>
<td>Increased proliferation and decreased apoptosis, appears to be part of hypoxia-mediated vascular response</td>
<td>48, 49</td>
</tr>
<tr>
<td>miRNA-27a</td>
<td>Involved in PPARγ pathway, increased expression propagates cellular proliferation</td>
<td>50</td>
</tr>
<tr>
<td>miRNA-138</td>
<td>Induces apoptosis resistance, endothelial dysfunction via blocking eNOS activation</td>
<td>51, 52</td>
</tr>
<tr>
<td>miRNA-150</td>
<td>Downregulated in PAH, prognostic value</td>
<td>53</td>
</tr>
<tr>
<td>miRNA-190</td>
<td>Regulates hypoxic vasoconstriction via potassium channels</td>
<td>54</td>
</tr>
<tr>
<td>miRNA-206</td>
<td>Decreased in hypoxia, part of HIF-1α pathway; decreased levels results in PASMC proliferation and decreased apoptosis</td>
<td>55, 56</td>
</tr>
<tr>
<td>miRNA-210</td>
<td>Hypoxia inducible, inhibits PASMC apoptosis</td>
<td>57</td>
</tr>
<tr>
<td>miRNA-328</td>
<td>Inhibited by hypoxia, suppression causes increased proliferation and vasoconstriction</td>
<td>58</td>
</tr>
<tr>
<td>miRNA-103/107</td>
<td>Inhibition in hypoxia leads to increased levels of HIF-1α, HIF-1β, and PASMC proliferation</td>
<td>59</td>
</tr>
<tr>
<td>miRNA-9</td>
<td>Increased in hypoxia, induces PASMC proliferation</td>
<td>60</td>
</tr>
</tbody>
</table>

Note: BMPR2: bone morphogenetic protein receptor type 2; BRD4: bromodomain 4; eNOS: endothelial nitric oxide synthetase; FGF2: fibroblast growth factor 2; HIF-1: hypoxia-inducible factor 1; miRNA: microRNA; PA: pulmonary arterial; PAEC: pulmonary arterial endothelial cell; PAH: pulmonary arterial hypertension; PASMC: pulmonary arterial smooth muscle cell; PPARγ: peroxisome proliferator-activated receptor gamma.
Interventional Therapy for PH
A. Contrast-enhanced lung CT before PTPA shows stenosis or occlusion of most of the pulmonary arteries without visualization of most of the peripheral capillary vessels.
B. Most pulmonary arteries are visualized, along with peripheral capillary vessels.

Pulmonary artery (PA) nerve distribution (Porcine model).

Documentation of circumferential distribution of nerves with differences in their vascular location with respect to the vessel lumen in a porcine model of acute PH.

Histology performed acutely after PA denervation showed that the ablation lesions were visible.

Vascular staining for nerve associated S100 protein was decreased indicating effective nerve injury.

Thus, it is clear that PA denervation results in nerve ablation and this corresponds to an acute decrease in PA tone and pressures.

Hemodynamic, Functional, and Clinical Responses to Pulmonary Artery Denervation in Patients With Pulmonary Arterial Hypertension of Different Causes

Phase II Results From the Pulmonary Artery Denervation-1 Study


DOI: http://dx.doi.org/10.1161/CIRCINTERVENTIONS.115.002837
Circulation: Cardiovascular Interventions. 2015;8:e002837
Originally published November 9, 2015
Results
Between April 2012 and April 2014, 66 consecutive patients with a resting mPAP ≥25 mmHg treated with PADN were prospectively followed up. Target drugs were discontinued after the PADN procedure.

Hemodynamic response and 6MWD were repeatedly measured within the 1 year post PADN follow-up.

The clinical end point was the occurrence of PAH-related events at the 1-year follow-up.

Circulation: Cardiovascular Interventions 2015;8e002837
A PA denervation (PADN) catheter with 10 electrodes is positioned at the distal MPA, with electrodes A, B, and C at points A, B, and C, respectively.

PA ablation was performed using a dedicated 7-F temperature-sensing ablation catheter. The details of the device and the PADN procedure have been previously described. Briefly, PADN was thereafter performed only in the periconjunctival area between the distal main trunk and the ostial left branch (points A, B, and C).

Shao-Liang Chen et al. Circ Cardiovasc Interv. 2015;8:e002837
Results

April 2012 to April 2014:

• 66 consecutive patients (resting mPAP ≥ 25 mmHg) treated with PADN were prospectively followed up. Target drugs discontinued after the PADN procedure.

• There were no PADN-related complications.

• Hemodynamic success = defined as the reduction in mPAP by a minimal 10% post PADN) was achieved in 94% of all patients.

• Mean absolute reduction in systolic PAP and mPAP within 24 hours of −10 mmHg and −7 mmHg, respectively.

• The average increment in 6-minute walk distance after PADN was 94 m.

• PAH-related events occurred in 10 patients (15%), mostly driven by the worsening of PAH (12%).

• 8 (12%) all-cause deaths, with 6 (9%) PAH-related deaths.

Circulation: Cardiovascular Interventions 2015;8e002837
**Right Heart Catheterization Measurements at Baseline and 6-Month and 1-Year Follow-Up**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Baseline (n=66)</th>
<th>6 mo (n=65)</th>
<th>1 y (n=56)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic PAP, mm Hg</td>
<td>86.6±28.9</td>
<td>71.6±25.8</td>
<td>70.1±27.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>53.1±19.1</td>
<td>44.8±16.4</td>
<td>44.6±17.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic PAP, mm Hg</td>
<td>34.8±15.1</td>
<td>29.9±14.2</td>
<td>28.4±13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>12.4±7.3</td>
<td>10.6±5.8</td>
<td>10.3±5.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Systolic RVP, mm Hg</td>
<td>85.1±28.4</td>
<td>75.3±29.7</td>
<td>72.9±29.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAOP, mm Hg†</td>
<td>14.7±11.7</td>
<td>12.4±5.3</td>
<td>11.8±5.2</td>
<td>0.075</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.3±1.2</td>
<td>4.0±1.1</td>
<td>4.1±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>13.2±6.9</td>
<td>8.4±5.8</td>
<td>8.3±6.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Indicated the comparison of baseline vs 6 mo; all variables were nonsignificantly different between 6 mo vs 1 y.
†Data were transferred to log data for analysis.
Pulmonary artery denervation for treatment of a patient with pulmonary hypertension secondary to left heart disease

Hang Zhang, Juan Zhang, Du-Jiang Xie, Xiaoming Jiang, Feng-Fu Zhang, and Shao-Liang Chen
Nanjing, Jiangsu 210006, China

Abstract

Pulmonary hypertension (PH) predicts poor outcome in patients with left heart disease. A 62-year-old man was referred for heart failure associated with ischemic cardiomyopathy. He received a diagnosis of combined postcapillary and precapillary PH secondary to left heart disease on the basis of hemodynamic parameters. After the pulmonary artery denervation procedure was performed, hemodynamic parameters were markedly improved, which resulted in a significant increase in functional capacity.

Keywords: pulmonary hypertension, heart failure, pulmonary artery denervation

Pulmonary hypertension (PH) predicts poor outcome in patients with left heart disease. PH associated with left heart disease (PH-LHD) occurs initially as pulmonary venous hypertension as a result of backward transmission of elevated left ventricular filling pressure. Over a period of time, pulmonary vasoconstriction and vascular remodeling result in sustained elevation of pulmonary vascular resistance. Currently, no specific therapy is available for PH-LHD. Pulmonary vasodilator drugs found effective for idiopathic pulmonary arterial hypertension have recently been tried in the treatment of PH-LHD, but the results are not very promising. Recently, the efficacy and the safety of pulmonary artery denervation (PADN) in treating patients with idiopathic pulmonary arterial hypertension has been reported. We successfully employed PADN in treating a patient with PH-LHD.
RCT conducted over 12 weeks in patients with IPAH.
- 16 patients were treated with conventional therapy.
- 15 patients additionally received an IV infusion of EPCs.
- 6MWD significantly (p<0.0001) improved in EPC-treated pts.
- mPAP, PVR and cardiac output were also improved.
- No serious adverse events in the EPC group.
Conclusions

- A national effort, led by NIH, should seek to coordinate bio-samples and bio-data from all funded programs to a web based repository so that information can be shared and correlated.
- Example programs include PVDOMICs, PHBI, the National Biological Sample and Data Repository for PAH and other projects where bio-samples are collected and biological data stored.
- Genomic data should be coordinated with the National Precision Medicine Initiative so that large genetic databases can be used to detect genotype-phenotype relationships.
- A taskforce of stakeholders to develop a Master Clinical Trials Protocol for PVD to apply precision medicine principles to future trials should be created.
- Development and testing of newer meaningful endpoints, both primary and secondary.
- Continued development of imaging, hemodynamic, cellular, genomic and metabolic variables that will identify patients for their individual features.
EXAMPLE:
120 patients with same mutation regardless of PH type):
20 patients each with:
- IPAH
- PSS
- HIV
- Liver disease
- “disproportionate PAH”
  - HFpEF
  - COPD
What about cost?
Future Therapeutic Pathways to Explore

- Prostacyclin
- Nitric oxide / cGMP
- Endothelin (including ECE inhibitors – Daglutril)
- PDE5
- Soluble guanylate cyclase activators - riociguat = stimulator, cinaciguat = activator…(Rio can stimulate reduced sGC. Cina can ACTIVATE sGC in its oxidized form or when the heme group is lost – both of these scenarios render sGC unresponsive to NO)
- NO-independent sGC activation (BAY 58-2667, HMR-1766 and S-3448)
- Enhancing NOS activity
- Enhancing eNOS transcription (AVE9488 and AVE3085)
- Natriuretic peptide (neutral endopeptidase) inhibition
- Adrenomedullin (activation of signaling pathways, such as cAMP, NO-cGMP and PI3K/Akt)
- VIP + neutral peptidase inhibition
- BMPR2-targeted treatment strategies
  - Repairing BMPR2 signaling
  - Rescue strategies using viral vectors
  - Rescue of trapped intracellular mutant BMPR2 protein (chemical chaperones (thapsigargin, glycerol or sodium 4-phenylbutyrate)
- TGF-β blockade / ALK5 inhibition (SB525334)
- Immune alteration / manipulation
Future Therapeutic Pathways to Explore

- Serotonin / serotonin transporter agonists
- Tryptophan hydroxylase 1 inhibition
- Antagonism of 5-HT2B and/or 5-HT2A receptors (Terguride, PRX-08066)
- Ranolazine
- Rho-kinase inhibition (Y-27632, fasudil)
- Restoration of potassium channels
- Inhibition of transcription factors (HIF-1α, NFAT, c-Jun) (PROMISING)
- Inhibition of transient receptor potential (trp) channels
- Inhibition of PDK isoforms (activating PDH and promoting glucose oxidation (dichloroacetate)
- Tyrosine kinase inhibition
- Serine/threonine kinase inhibition (Raf family and downstream pathways)
- Elastase inhibition (synthetic inhibitors w/o toxicity yet to be developed)
- HDAC inhibition
- Augmentation of endogenous elastin inhibitors (eg, elafin)
- PPAR agonism / nitro-fatty acids
- Apelin
- EPC administration
- Gene therapy - Vectors expressing prostacyclin synthase, endothelial NOS, or VEGF (see above)
Eight patients died during the 12-week study. All were in the conventional-therapy group. (P = 0.003)

36 year-old woman with IPAH
• Failed therapy with three oral agents

• 6MW 120 m  BNP = 1606 pg/mL

• RHC: mRAP = 22 mm Hg  CI = 1.3 L/min/m²

• Listed for lung transplant

• IV epoprostenol initiated

• Significant improvement over 14 days (sx / activity / RV fnc)

• BNP 1606 ñ 402 pg/mL
4 MONTHS AFTER DISCHARGE

[Image of an ultrasound scan with various technical details]

3V2c S 64Hz
H4.0MHz 140mm
Echo
NTHI General

68dB T1/-1/1/1/4
Gain= 11dB Ω=1

Store in progress
0:41:36
HR= 80bpm
The VITAL Trial*

HR 0.12
95% CI (0.08, 0.17)
P = 0.000001

Tapson VF, et al. NEJM 2017

* Vlc and Tony Hage And Mike Lewis Trial
CONCLUSIONS

• The mortality of PAH has decreased
• However, it remains high
• The diagnosis of PH / PAH is still made too slowly
• Medical therapy for PAH continues to advance
• Interventional therapy may advance PAH / PH therapy also
• PH is entering the precision medicine era – we need data banks and carefully designed trials
• Stay tuned for stem cell trials
• No one should die without IV prostanoid therapy
Thank you!
Vic Tapson
victor.tapson@cshs.org
Cell: 919-971-6441
Without lungs

Of all of the organs the lung,
Is the hero that seems most unsung.
Without it your hue
Would be some shade of blue,
And there wouldn't be much past your tongue.

With no way to breathe in your air,
Pneumonia would be very rare.
Your X-ray if done,
Would be only for fun,
If just bones and a heart were in there.

The oxygen breathed I suppose,
Wouldn't go where it usually goes.
It would end up instead,
In your gut or your head,
Causing flatus from belly and nose.
Dyspnea would not be a word. The thought of a rhonchus absurd. That tool of Laënnec, Would be the subject, Of inventions that never occurred.

The lung cells are somewhat unique. We have grants to sort out their mystique. There’s Type One and Type Two, I forget what they do, I’m a clinician and not a lab geek.

Without a liver or brain you’d be had. And you need both a heart and gonad. But no lungs? The anguish, Of being a fish, And of saying, “That flounder's my dad!”

PPH, IPF, LAM, CF, COPD and green phlegm. BOOP, CPAP, PEEP, ARDS in lab sheep, We’d never see any of them.
Without lungs we'd have no Philharmonic. 
Having sex would at best be platonic. 
With a real strong attraction, 
Perhaps some quick action, 
More likely we'd be anhedonic.

Your thinking would reach an impasse. 
If you couldn't breathe in and out gas. 
Because CO$_2$, 
Couldn't go down if you, 
Had to exhale it out through your bum.

Well, one final thought, one detail. 
Without lungs, respiration would fail. 
Could you breathe your last breath? 
And go on to your death... 
If you didn't have lungs to inhale?

Victor F Tapson
Duke University Medical Center, Durham, NC, USA
THANK YOU!!!!
Sunrise – Sabi Sabi, South Africa

Thank you!
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